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Stereotactic body radiotherapy for oligo-metastatic liver disease – Influence of pre-treatment chemotherapy and histology on local tumor control

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ABSTRACT

Introduction: Stereotactic body radiation therapy (SBRT) is applied in the oligometastatic setting to treat liver metastases. However, factors influencing tumor control probability (TCP) other than radiation dose have not been thoroughly investigated. Here we set out to investigate such factors with a focus on the influence of histology and chemotherapy prior to SBRT using a large multi-center database from the German Society of Radiation Oncology.

Methods: 452 SBRT treatments in 363 patients were analyzed after collection of patient, tumor and treatment data in a multi-center database. Histology was considered through random effects in semi-parametric and parametric frailty models. Dose prescriptions were parametrized by conversion to the maximum biologically effective dose using alpha/beta of 10 Gy (BED_{max}).

Results: After adjusting for histology, BED_{max} was the strongest predictor of TCP. Larger PTV volumes, chemotherapy prior to SBRT and simple motion management techniques predicted significantly lower TCP. The model predicted a BED of $209 \pm 67\ Gy_{10}$ necessary for 90% TCP at 2 years with no prior chemotherapy, but $286 \pm 78\ Gy_{10}$ when chemotherapy had been given. Breast cancer metastases were significantly more responsive to SBRT compared to other histologies with 90% TCP at 2 years achievable with BED_{max} of $157 \pm 80\ Gy_{10}$ or $80 \pm 62\ Gy_{10}$ with and without prior chemotherapy, respectively.

Conclusions: Besides dose, histology and pretreatment chemotherapy were important factors influencing local TCP in this large cohort of liver metastases. After adjusting for prior chemotherapy, our data add to the emerging evidence that breast cancer metastases do respond better to hypofractionated SBRT compared to other histologies.

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Stereotactic body radiation therapy (SBRT) has evolved as the guideline recommended treatment for inoperable patients with stage I NSCLC [1] and can safely be offered to operable patients who decline surgery [2]. Fostered by this evolution and by technical advances in delivery technology including sophisticated motion management methods and image-guided radiotherapy, its use has been expanded to virtually all body sites.

Although SBRT has been established for liver metastases as early as for lung cancer, small sampled prospective phase I/II trials and only slightly larger retrospective reports have been published. One of the reasons is that many different non-surgical local ablative treatment strategies have emerged at the same time competing at a similar patient population as SBRT. Data prospectively comparing these treatment options are largely lacking.

To overcome the limitations of small sized retrospective research reports, we implemented the multi-center SBRT database initiative within the German Society of Radiation Oncology (DEGRO) to collect data on SBRT treatments and outcomes from

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different radiation centers experienced in SBRT. With these data, it is possible to increase statistical power for modeling purposes to derive predictive factors of local failure and overall survival in order to establish recommendations regarding patient selection, dose prescription and fractionation.

The focus of this analysis is to establish a dose–response relationship based on the biological effective dose (BED) and to investigate the influence of histology and pre-SBRT chemotherapy on local control of liver metastases treated with SBRT. A detailed radiobiological modeling of these respective factors will be presented, and the possible impact for dose selection will be discussed.

Materials and methods

Dataset

Our analysis is based on a multi-center SBRT database within the framework of the German Society of Radiation Oncology (DEGRO) and consists of 623 liver metastases in 464 patients treated with SBRT at 17 German and Swiss institutions between 1997 and 2015. This database was designed as a SBRT patterns-of-care database within the DEGRO initiative and headed by the DEGRO SBRT working group. Primary inclusion criteria were patients treated with SBRT for liver metastases from any histology-proven primary solid tumor. The participating centers used – based on available technology, tumor size and location in correlation to organs-at-risk – a center-specific fractionation schedule. A detailed description of patient, tumor and treatment characteristics was collected retrospectively and collated in a tabular data structure. The multicenter data collection and analysis was approved by the Ethics committee of the Kanton Zurich, Switzerland (BASEC-Nr. 2016-00744). The data collection of the individual participating centers was approved according to local regulations by the respective local ethics committees.

The number of fractions ranged between 1 and 13 (median 3). Most treatments were planned with inhomogeneous dose distributions with PTV encompassing doses most frequently prescribed to the 80% isodose line (32% of all SBRT treatments). While the prescribed and maximum PTV doses were available for all patients, the mean GTV dose was missing for 61% of treatments. Due to missing data for several patient and treatment characteristics we here concentrated on variables that were available for ≥80% of the recoded treatments and removed observations with missing information. The resulting sample consists of 452 treatments of 363 patients with complete information on time of last follow-up, tumor recurrence (yes/censored), age, gender, chemotherapy within 3 months prior to SBRT (yes/no), dose algorithm used for treatment planning (pencil beam/more advanced algorithms), histology and PTV volume. The PTV rather than the GTV or CTV based volumes was chosen as a surrogate for tumor volume, because it was missing for only 75 metastases while the latter were missing for 302 metastases. The motion management technique was categorized into simple (free breathing, abdominal compression) versus advanced (breath-hold, gating, tracking) techniques. Only histological subtypes with more than 20 SBRT treatments were considered as distinct classes for modeling; the remainder was grouped together into the class "other". Local failure of a metastatic lesion was defined as either reappearance after complete remission or re-growth after initial partial response in follow-up CT or MRI scans. PET-CT scans were used by only a few centers in equivocal cases to confirm local recurrence, usually under the conditions that (a) a pre-therapeutic PET-CT was available, (b) time since SBRT was more than 12 months and (c) dynamics of SUVmax rose above twice the normal liver SUV or above the pre-treatment levels [3]. Confirmatory biopsies in case of radiological diagnosis of local recurrences were not routinely performed. Table 1 provides an overview of the patient and treatment characteristics of our sample.

Local tumor control probability (TCP) model specification

This analysis focused on the cause-specific hazard of local failure only. Death was considered a competing event and handled the same as the usual censorings. Modeling was performed per metastasis rather than on a per patient basis. Because there are many different metastases subtypes, we did not include histology as a fixed effect in a Cox proportional hazards model as this could require too many parameters to be estimated, leading to a breakdown of asymptotic assumptions and possibly overestimating the effects of certain histological subtypes [4]. Furthermore, it would not allow computation of the variability between these subtypes. Such variability can arise due to unobserved factors that we are not able to explicitly model, such as genetic heterogeneity. Frailty models allow to take unobserved heterogeneity into account when modeling time-to-event data [4–6]. We therefore used shared frailty models in which the metastases were grouped according to their histology into "clusters", with all metastases in a cluster sharing the same association between the risk of recurrence and any unobserved factors. These associations are known as "frailties" or "random effects" and modeled as random variables drawn from a parametric probability distribution [4,6]. We used two types of shared frailty models, a parametric and a semi-parametric one. The latter is also known as a mixed effects Cox model [5]

$$h_{ij}(t) = h_0(t)\exp(\boldsymbol{x}_{ij}^T\boldsymbol{\beta} + w_i) \tag{1}$$

where $h_{ij}(t)$ is the conditional hazard function for the jth metastasis from the ith cluster ($j = 1, \ldots n_i, i = 1, \ldots, s$), $h_0(t)$ the baseline hazard, w_i the random effect for the ith cluster, $\boldsymbol{x}_{ij}^T = (x_{ij1}, \ldots, x_{ijp})$ the p fixed effects covariates and $\boldsymbol{\beta}$ their corresponding regression coefficients. The frailties $\exp(w_i)$ act as factors by which the baseline hazard function is multiplied; metastases in a cluster with a negative or positive random effect have a lower and higher risk of recurrence, respectively, than an average metastasis which has $w_i = 0$.

In Eq. (1) the random effects are assumed to stem from a normal distribution, $w_i \sim N(0, \gamma)$, with mean 0 and variance γ. Estimates for $\boldsymbol{\beta}$ and γ can then be obtained by maximizing a penalized partial likelihood function; for more details see Therneau et al. [5] or chapter 5.2 in Duchateau and Janssen [4].

A parametric shared frailty model was used in order to translate the heterogeneity between the different histological subtypes quantitatively into the spread of TCP from cluster to cluster. We specified a Weibull distribution for the event times such that the baseline hazard function could be expressed as $h_0(t) = \lambda\rho t^{\rho-1}$ with scale parameter $\lambda > 0$ and shape parameter $\rho > 0$. We further specified a gamma frailty distribution with mean one and variance θ, which relates to the variance of the random effect w_i for cluster i from Eq. (1) according to $\gamma = \psi'(1/\theta)$ with ψ' the trigamma distribution (chapter 5.2.4 in [4]). Fitting this model to the data, the tumor control probability after time t in cluster i can be estimated as

$$\hat{S}_i(t) = \exp(-\hat{\lambda}t^{\hat{\rho}}\exp(\boldsymbol{x}_{ij}^T\boldsymbol{\beta} + w_i)). \tag{2}$$

All covariates given in Table 1 were incorporated as fixed effects into the models, except for number of fractions and prescribed and maximum PTV dose. Instead, we used $\mathrm{BED}_{\max}$, for which we have previously shown that it correlates better with local control than the PTV encompassing BED [7,8]. Eq. (2), was used to estimate the dose needed to achieve a certain TCP at a specified follow-up time, and standard errors were derived from bootstrapping the data 100 times.

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Table 1
Patient and treatment characteristics for our sample of 363 patients with 452 SBRT treatments.

Characteristic	Absolute count	Percent	Median	Range
Age [years]			64	15–93
Gender				
Male	206	56.7		
Female	157	43.3		
Chemotherapy prior to SBRT				
Yes	354	78.3		
No	98	21.7		
PTV volume [ccm]			70.4	4.5–1074.0
Histology of primary tumor				
Cholangiocellular Carcinoma	43	9.5		
Colorectal Cancer	203	44.9		
Breast cancer	56	12.4		
NSCLC	28	6.2		
Pancreatic cancer	20	4.4		
Ovarian cancer	20	4.4		
Other	82	18.1		
Motion management				
Simple	296	65.5		
Advanced	156	34.5		
Dose calculation algorithm				
Pencil beam	181	40.0		
Advanced	271	60.0		
Number of fractions			3	1–13
Prescribed dose per fraction [Gy]			9.9	2.1–28
PTV max dose [Gy]			13.6	3.0–42.1
BED_{max} [Gy_{10}]			129.6	38.5–292.4

BED_{max}: Maximum Biologically effective dose to the tumor assuming $\alpha/\beta = 10$ Gy. Motion management has been categorized into simple (free breathing, abdominal compression) and advanced (breath hold, gating, tracking). Chemotherapy specifically addresses chemotherapy given for metastatic disease, within 3 months prior to SBRT.

Analysis was performed using R version 3.1.3 with the coxme package for fitting the semi-parametric mixed effects Cox model (Eq. (1)) and the parfm package [9] for fitting the parametric frailty model (Eq. (2)). Since models were nested, differences between the fixed and mixed effects Cox models were assessed using the maximum likelihood ratio test. In addition the difference in the second-order bias corrected Akaike Information Criterion (AIC_C) was used for model comparison, with a difference of $\Delta AIC_C > 4$ indicating that the model with the smaller AIC_C value should be preferred [10]. Prior to model fitting, all numeric covariates (BED, age, tumor volume) where rescaled to mean 0 and standard deviation 0.5 to set them on the same scale as the categorical covariates which were coded as 0 and 1 [11].

Results

Median overall survival of all patients was 20.8 months (95% CI 17.7–24.9 months). The actuarial survival rate was 71% (67–77%) and 45% (39–51%) at one and two years, respectively. For the 452 treated liver metastases, 100 local recurrences were observed up to 43.1 months (crude rate 22.1%). The estimated one, two and three year local control estimates according to Kaplan–Meier were 78% (95% CI 74–83%), 64% (58–71%) and 60% (53–68%), respectively (Fig. 1A).

Overall, a clear dose–response relationship was present over the range of the fractionation schemes used after conversion to BED_{max}: without taking confounding factors into account a BED_{max} of 102 ± 23 Gy_{10} and 192 ± 37 Gy_{10} was necessary to achieve a local control of at least 80% and 90%, respectively, at 1 year.

The univariate frailty model (Eq. (1)) resulted in a significantly better fit than the Cox model ($p = 0.00494$, $\Delta AIC_C = 7.9$), suggesting that neglecting heterogeneity among metastases could lead to biased estimates of the regression coefficients. Indeed, without adjusting the Cox model for histology, BED_{max} was not as strong a predictor for local tumor control as anticipated (Supplementary Table 1). Only after adjusting for histology, BED_{max} became the most significant predictor as expected. Thereby every increase by 42.1 Gy_{10} (one standard deviation) was associated with a 28% decreased risk of recurrence (HR = 0.72, 95% CI = [0.56,0.91]). Besides BED_{max}, the PTV volume, tumor histology, chemotherapy prior to SBRT, dose calculation algorithm and motion management method were all significantly associated with local TCP in both the fixed and the mixed effects Cox model (Supplementary Table 1). Thereby, significant correlations between BED_{max}, PTV volume and motion management technique were present (larger volumes and less advanced motion management techniques associated with lower dose; larger PTV volumes associated with less advanced motion management). These and other correlations between the covariates are given in Supplementary Table 2. These correlations did not translate into high multicollinearity in the model, however, as indicated by small values ($\lesssim 1.2$) of the variance inflation factors.

Fig. 1B shows the Kaplan–Meier curve for local tumor control of all metastases stratified according to chemotherapy treatment prior to SBRT. Patients with chemotherapy prior to SBRT had a significantly reduced local control at two years, 58% (51–67%) vs 83% (74–93%).

The effect of histology on TCP is shown in Table 2, which provides the random effect estimates in descending order together with the corresponding hazard ratios and 95% CIs. The estimated variance parameter was $\gamma = 0.470$. Among the different histological subtypes, metastases originating from breast cancer stood out as the ones with the highest TCP in relation to BED_{max}, the effect reaching statistical significance ($p = 0.033$). On the contrary, pancreatic cancer and colorectal histology tended to have a worse local control, although this effect did not reach statistical significance ($p = 0.072$ and $p = 0.159$). The interpretation of the random effect estimates as relative risks thus suggests that – everything else being equal – patients with metastases originating from breast cancer had a 58% lower risk of recurrence than the average metastasis, while in contrast metastases from pancreatic and colorectal cancers had a 154% and 59% higher risk of recurrence. Note,

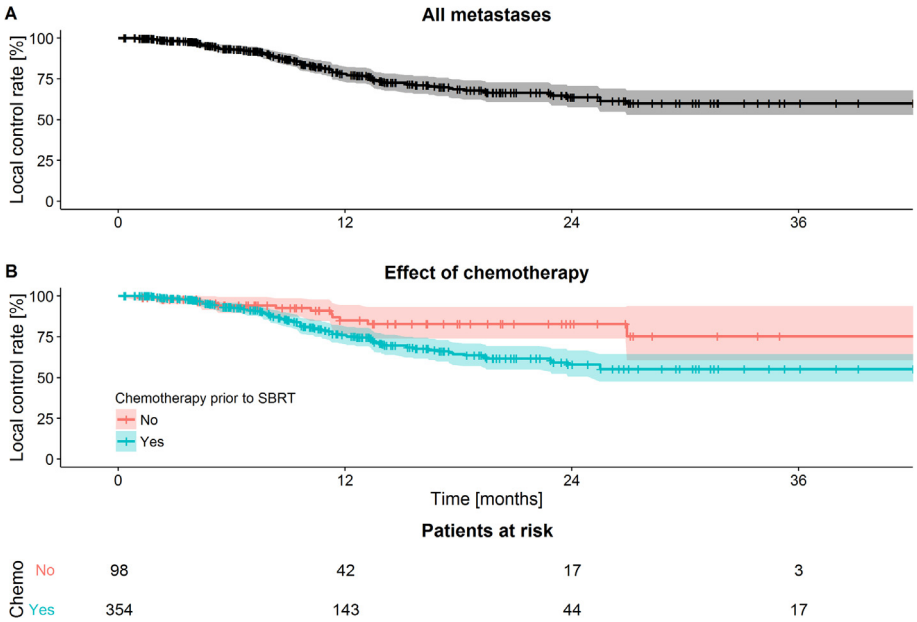

Fig. 1. Kaplan–Meier plots for all metastases without stratification (A) or stratified by chemotherapy prior to SBRT (B). The shaded areas represent 95% confidence intervals.

Table 2
Random effects estimates for the univariate frailty model. CCC: Cholangiocarcinoma; CRC: Colorectal carcinoma; BC: Bronchial carcinoma. The hazard ratios (HR) measure the relative risk of local tumor recurrence compared to an average metastasis if all observed covariates are assumed equal.

Histology	w_0	*p*-Value	HR	95% CI
Pancreas	0.931 ± 0.518	0.072	2.54	[0.92,7.00]
CRC	0.463 ± 0.329	0.159	1.59	[0.83,3.03]
Other	0.111 ± 0.378	0.769	1.12	[0.53,2.34]
Ovarian	−0.120 ± 0.477	0.801	0.89	[0.35,2.26]
BC	−0.150 ± 0.474	0.752	0.86	[0.34,2.18]
CCC	−0.375 ± 0.446	0.400	0.69	[0.29,1.65]
Breast	−0.860 ± 0.403	0.033	0.42	[0.19,0.93]

however, that especially the latter numbers possess quite large uncertainties (Table 2). The different radiation responses of colorectal and breast cancer metastases are also reflected in the Kaplan–Meier TCP estimates stratified by histology (Supplementary Figure 1) yielding actuarial 2-year local control rates of 51% (95% CI 42–62%), 88% (77–100%) and 73% (63–85%) for colorectal, breast and other metastases.

Next, we investigated the dependence of TCP from the applied BED_{max}, again stratified according to chemotherapy prior to SBRT. Fig. 2 shows the two-year tumor control rate as a function of BED_{max} for colorectal and breast cancer subtypes as well as the average metastasis. Regardless of pre-SBRT chemotherapy, there was a significant difference between the local control rate of breast cancer and colorectal histology across the whole dose range, with a larger spread in the lower dose area and a convergence toward higher doses. For patients with no prior chemotherapy, there was a predicted discrepancy of 26% and 18% tumor control rate between breast and colorectal cancer histology for a BED of 100 Gy_{10} and 150 Gy_{10}, respectively. For patients who received prior chemotherapy, this discrepancy at the same dose levels was even more pronounced with 40% and 31% local control rate.

When no prior chemotherapy was given, the dose needed to achieve at least 90% tumor control rate was 80 ± 62 Gy_{10} for breast cancer compared to 257 ± 74 Gy_{10} for colorectal cancer. Given this large TCP difference between metastases of breast cancer and

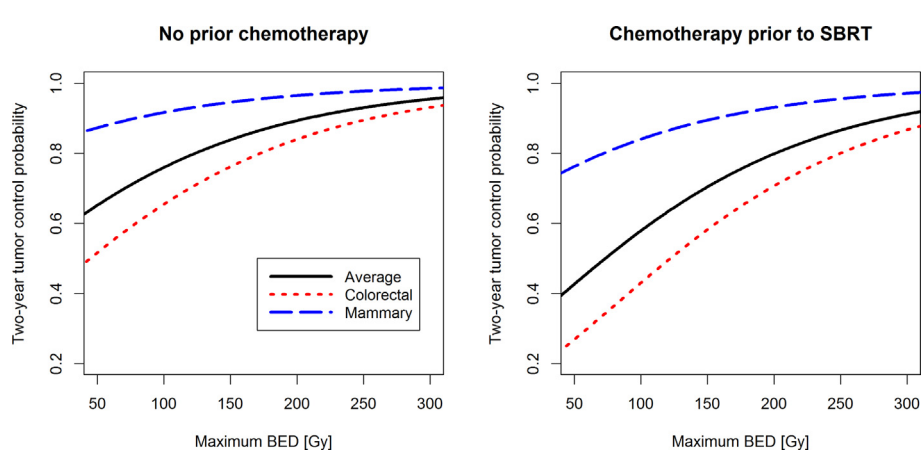

Fig. 2. Density distribution of one-year and two-year TCP over clusters stratified by chemotherapy prior to SBRT. All other covariates were set to their mean for plotting (corresponding to the mean age of 64 years, BED_{max} = 129 Gy_{10} and 110 ccm PTV volume).

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colorectal cancer, we refitted a Cox proportional hazards model, now including breast and colorectal histology versus all others as fixed effects covariates. The regression coefficient estimates for this model where similar to those of the univariate frailty model (Supplementary Table 1), with BED_{max} again showing the strongest correlation to the outcome ($\hat{\beta}_{BED_{max}} = -0.645$, $p = 0.007$). The effects of histology were estimated as 0.463 ± 0.251 ($p = 0.065$) for colorectal carcinoma and -1.116 ± 0.447 ($p = 0.013$) for breast carcinoma which had the second-strongest association with local control. Finally, the same model was fit to the female subset of patients consisting of 160 cases with 42 events. This subset included 63 and 54 metastases of colorectal and breast origin, respectively. Interestingly, BED_{max} ($\hat{\beta}_{BED_{max}} = -0.914$, $p = 0.017$) and breast histology ($\hat{\beta}_{MC} = -1.135$, $p = 0.023$) were the only significant predictors now, while chemotherapy ($\hat{\beta}_{chemo} = 1.072$, $p = 0.094$) and colorectal histology ($\hat{\beta}_{CRC} = 0.652$, $p = 0.106$) did not reach statistical significance.

Discussion

The aim of this study was to determine the influence of SBRT dose, cancer type and chemotherapy given prior to SBRT and their interactions on the response to SBRT among liver metastases. With respect to dose–response modeling our current analysis is unique as it represents the largest collection of liver metastases with in total 22 different histological subtypes treated with SBRT, although most of these consisted of very few cases and were grouped together into one class. However, for seven distinct histological classes sufficient data were available for modeling heterogeneity in TCP using frailty models in which histology is treated as a random rather than a fixed effect, allowing sufficient power for robust dose–response modeling and subgroup confounding factor analysis, like histology or pre-SBRT chemotherapy.

Dose–response relationship

Radiation dose as the most significant predictor of local control is an expected, but also reassuring result indicating plausibility of our multi-institutional database. The large variety in the number of fractionations (range 1–13) allowed us to exploit a wide range of BED_{max} values for modeling.

Few attempts for dose–response analysis or modeling have been published so far [12]. In heavily pretreated patients with predominantly metastases from colorectal carcinoma, Lanciano et al. [13] reported a local control rate at two years of 75% for a BED > 100 Gy compared to only 38% with lower doses. After dose escalation from 4×10 Gy to 3×15 Gy to the PTV periphery corresponding to a BED of 80 Gy_{10} and 112.5 Gy_{10}, respectively, Vautravers-Dewas et al. [14] observed an increase in local control rate from 86% to 100% at 1 year. The first true dose–response modeling has been published by Chang and colleagues for colorectal only metastases [15], followed shortly thereafter by Stinauer et al. [16] for melanoma and renal cell carcinoma metastases using a logistic tumor control probability model. BED of 90 Gy_{10} yielded a local TCP of 80% in colorectal cancer metastases, whereas 110 Gy_{10} were required for melanoma and renal cell cancer metastases.

In our analysis, a consistent dose–response relationship was observed, which was valid for the whole range of fractionation schedules after conversion to BED. Our analysis further implies that for an average metastasis without prior chemotherapy a PTV maximum BED of more than 124 ± 63 Gy_{10} is necessary to achieve 80% local control at two years; this increases to more than 209 ± 67 Gy_{10} PTV maximum BED in order to reach 90% local control (Fig. 2, Supplementary Table 2).

Using PTV BED_{max} in our current analysis as a surrogate for the dose delivered to the tumor was chosen for two reasons: 1. it is a robust dosimetric value and rather independent of the dose calculation algorithm [17] or motion management and target volume concept used [18]. 2. As SBRT is mostly prescribed inhomogeneously with a dose maximum within the PTV between 120–150% of the PTV encompassing dose (most frequently 125% in our database), the steep dose gradient within the PTV margin and the high dose plateau within the GTV/ITV seem more relevant for effective local control [19]. These results are in line with recently published reports by Swaminath et al. and Andratschke et al. indicating that the dose to the GTV is the more relevant dosimetric parameter for local control in gantry-based [20] or robotic [21] radiosurgery compared to PTV minimum dose. Nevertheless, this indicates the necessity of standardization of SBRT prescription and reporting in order to truly compare different SBRT schedules in a meaningful way. Especially, the ICRU report on SBRT prescription and reporting is eagerly awaited in this respect which will be an important step toward harmonizing SBRT schedules.

Besides dose several other variables were significantly correlated with local TCP, indicating better outcome for smaller tumors and advanced motion management techniques and dose calculation algorithms. This was despite significant correlation between each other, which is expected to increase the uncertainty of the individual regression coefficients. For example, although PTV size and motion management technique were correlated, the PTV effect on TCP is predominantly a function of tumor cell density/count as GTV size and PTV size were correlated.

The effect of pre-SBRT chemotherapy

Without controlling for histology, the influence of chemotherapy on local TCP was larger than SBRT dose expressed as BED_{max}, possibly induced by the high correlation between chemotherapy and histology (Supplementary Table 2). Indeed, there was a significant improvement in the TCP model fit when histology was accounted for as a random effect. A significantly larger proportion of metastases with colorectal (chemotherapy in 84.2% of cases) and breast cancer histology (83.9%) received chemotherapy prior to SBRT compared to other histological subtypes (70.5%, $p = 0.003$). As summarized in Supplementary Table 3, our model predicts that metastases treated with prior chemotherapy would require substantially higher radiation doses to achieve the same level of TCP. It is important to note that chemotherapy prior to SBRT was also associated with worse TCP in a similar database of pulmonary metastases [22].

There are several hypotheses for the effect of chemotherapy prior to SBRT on TCP. As PTV definition was based primarily on the GTV with an additional margin for organ movement and/or setup uncertainty, macroscopic tumor shrinkage after pre-SBRT chemotherapy may have yielded smaller PTV volumes with marginal miss of a microscopic invasion front surrounding the visible metastases. Then the marginal PTV dose and the steep gradient outside the PTV may not have been sufficient for sterilizing the microscopic tumor spread. As we are missing this specific information – whether or not metastases were responding to chemotherapy prior to SBRT – we were not able to test this hypothesis on our dataset.

Another explanation is that surviving tumor cells after chemotherapy are more likely to be resistant to another cytotoxic insult or have acquired improved DNA repair capacity [23], ultimately switching to or selecting for a more radioresistant phenotype. Similar reasoning has been put forward to explain the generally more aggressive behavior of metastatic disease if adjuvant chemotherapy had been given during treatment for the primary tumor [24].

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The influence of histology on tumor control probability

Our data indicate significant heterogeneity among liver metastases of different histological subtype (Fig. 2) that – if not adjusted for – could lead to biased effect estimates for important covariates. Such heterogeneity may arise from the genetic heterogeneity between different tumor types. A recent assessment of radiosensitivity in 372 liver metastases based on an index defined through the expression of 10 individual genes [25] predicted pancreatic neuroendocrine metastases and colorectal adenocarcinoma metastases to be more radioresistant than other histologies such as breast or lung adenocarcinoma. Though an intriguing finding, the small sample size of that study precluded robust dose–response modeling to validate the hypothesis on their clinical SBRT dataset. Although CRC metastases exhibited an inferior local control compared to non-CRC metastases in our survival analysis, the respective radiosenisitivity index of some non-CRC metastases would indicate an even more radioresistant phenotype.

Several previous studies about SBRT treatment of pulmonary metastases reported worse local control rates for colorectal histology [26–28], while others did not [29–31]. These studies generally had small sample sizes and accordingly not enough statistical power to investigate the interplay of several prognostic factors with histology in multivariable analysis. One of the most important confounding factors for local control appears to be pre-SBRT chemotherapy, as shown in our study. As chemotherapy was most likely administered in most CRC metastases, the finding of a more resistant phenotype in the previously mentioned studies may be a consequence of this confounding factor which had not been taken into account rather than a consequence of an intrinsic radioresistance of CRC metastases.

We previously conducted a similar dose–response modeling effort of lung metastases [32] where histology was also incorporated by random effects, although in a logistic regression model. Here we used mixed effects Cox models instead of logistic regression, in this way accounting for censoring and follow-up time as well. For the lung we had found no difference with respect to the dose needed to achieve 90% TCP of an average metastasis compared to CRC metastases [32]. Although this former analysis did not account for censoring, its results are expected to be robust in the high-dose region of the TCP curve where censored observations are most probably equivalent to long-term tumor control. We confirmed this by re-analyzing the lung metastases data using the semi-parametric mixed effects Cox model with BED at the isocenter as the sole predictor: in a total of 769 lung metastases with median follow-up time of 11.3 months (range 0.13–124.8 months), CRC histology was associated with a hazard ratio of 0.97 (95% CI = [0.56,1.66], $p = 0.903$).

In contrast to CRC and other metastases, liver metastases from breast cancer exhibited a significantly higher TCP over the whole dose range, regardless of confounding factors such as pre-SBRT chemotherapy. More interestingly, the results for breast cancer metastases were comparable in our datasets for liver and lung metastases, as a re-analysis of the latter with the mixed effects Cox model revealed a reduced risk of local failure for breast cancer histology as well (HR = 0.58, 95% CI = [0.28,1.25], $p = 0.166$). This finding is also in agreement with the observation of Milano et al. [33] in a series of oligometastatic patient treated with SBRT showing a better local control for breast cancer metastases in different organs, even at lower cumulative doses.

Based on these observations we conclude that breast cancer metastases do respond better to hypofractionated stereotactic radiotherapy and exhibit a higher TCP compared to metastases from other primaries. This adds to the emerging evidence that breast cancer may be particularly well suited for SBRT in oligometastatic disease as high local control with reasonable ablative doses can be achieved while minimizing toxicity with this approach. A causative explanation cannot be drawn from the current data, but our results are in line with recent analyses of hypofractionated post-lumpectomy data suggesting that breast cancer could have a lower α/β ratio of around 4 Gy, significantly lower than anticipated for most other solid tumors [34]. If this is the case, our calculations in which we used $\alpha/\beta = 10$ Gy would have significantly underestimated the BED and this would explain the high TCP at lower BED_{10} compared to other solid tumors in our dataset. As there is considerable uncertainty to tumor specific BED values, we used an α/β ratio of 10 Gy for all tumor entities in our analysis.

Although our results are robust with regard to statistical methodology and highly relevant for SBRT practice, we are well aware of the limitations inherent to our retrospective data collection including missing information, correct data validation, non-standardized follow-up and patients lost to follow-up. Still, as no large-scale prospective data are available our data represent the most comprehensive data registry, which allows for reliable modeling of dose–response and predictive factors.

Conclusions

A clear dose–response relationship has been observed in our large cohort of liver metastases from different histologies. Besides dose, histology and pre-SBRT chemotherapy were important factors strongly influencing local tumor control. Probably no differing TCP of CRC metastases compared to other histologies exists; increased radiation resistance of CRC metastases as reported in some studies may rather reflect the higher resistance after pre-SBRT chemotherapy. In contrast, breast cancer metastases showed a significantly more favorable TCP over the whole dose–response spectrum regardless of confounding factors, contributing to emerging evidence that this subtype might be particularly radiosensitive to high doses per fraction as in SBRT. Since models based on retrospective data can only guide in the formulation of hypothesis, prospective trials are needed to determine the proper dose selection of SBRT for oligometastatic disease.

Precis

Stereotactic irradiation of liver metastases yields a strong dose–response relationship that is modified by factors such as chemotherapy and metastases histology. Breast cancer metastases respond better to treatment while chemotherapy given prior to treatment has a negative effect on local tumor control.

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Author contributions

RJK, NA and MG drafted the manuscript. RJK and NA analyzed and interpreted the data. All other authors took part in the data collection, interpretation procedure, drafting and reviewing of the article.

Author statement

All authors approved the presented article before submission.

Conflict of interest

NA confirms that all authors have nothing to declare at the time of submission.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2017.01.013.

References

[1] Vansteenkiste J, Crinò L, Dooms C, Douillard JY, Faivre-Finn C, Lim E, et al. 2nd ESMO consensus conference on lung cancer: Early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. Ann Oncol 2014;25:1462–74.
[2] Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol 2015;16:630–7.
[3] Stinauer MA, Diot Q, Westerly DC, Schefter TE, Kavanagh BD. Fluorodeoxyglucose positron emission tomography response and normal tissue regeneration after stereotactic body radiotherapy to liver metastases. Int J Radiat Oncol Biol Phys 2012;83:e613–8.
[4] Duchateau L, Janssen P. The frailty model. 1st ed. New York: Springer Science +Business Media; 2008.
[5] Therneau TM, Grambsch PM, Pankratz VS. Penalized survival models and frailty. J Comput Graph Stat 2003;12:156–75.
[6] Wienke A. Frailty models in survival analysis (PhD dissertation). Martin-Luther-Universität Halle-Wittenberg; 2007.
[7] Guckenberger M, Klement RJ, Allgäuer M, Appold S, Dieckmann K, Ernst I, et al. Applicability of the linear-quadratic formalism for modeling local tumor control probability in high dose per fraction stereotactic body radiotherapy for early stage non-small cell lung cancer. Radiother Oncol 2013;109:13–20.
[8] Klement RJ, Allgäuer M, Appold S, Dieckmann K, Ernst I, Ganswindt U, et al. Support vector machine-based prediction of local tumor control after stereotactic body radiation therapy for early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2014;88:732–8.
[9] Munda M, Rotolo F, Legrand C. Parfm: parametric frailty models in R. J Stat Softw 2012;51:1–20.
[10] Burnham KP, Anderson DR. Multimodel inference: understanding AIC and BIC in model selection. Sociol Methods Res 2004;33:261–304.
[11] Gelman A. Scaling regression inputs by dividing by two standard deviations. Stat Med 2008;27:2865–73.
[12] Wulf J, Guckenberger M, Haedinger U, Oppitz U, Mueller G, Baier K, et al. Stereotactic radiotherapy of primary liver cancer and hepatic metastases. Acta Oncol 2006;45:838–47.
[13] Lanciano R, Lamond J, Yang J, Feng J, Arrigo S, Good M, et al. Stereotactic body radiation therapy for patients with heavily pretreated liver metastases and liver tumors. Front Oncol 2012;2:23.
[14] Vautravers-Dewas C, Dewas S, Bonodeau F, Adenis A, Lacornerie T, Penel N, et al. Image-guided robotic stereotactic body radiation therapy for liver metastases: is there a dose response relationship? Int J Radiat Oncol 2011;81:e39–47.
[15] Chang DT, Swaminath A, Kozak M, Weintraub J, Koong AC, Kim J, et al. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. Cancer 2011;117:4060–9.
[16] Stinauer MA, Kavanagh BD, Schefter TE, Gonzalez R, Flaig T, Lewis K, et al. Stereotactic body radiation therapy for melanoma and renal cell carcinoma: impact of single fraction equivalent dose on local control. Radiat Oncol 2011;6:34.
[17] Haedinger U, Krieger T, Flentje M, Wulf J. Influence of calculation model on dose distribution in stereotactic radiotherapy for pulmonary targets. Int J Radiat Oncol Biol Phys 2005;61:239–49.
[18] Guckenberger M, Wilbert J, Krieger T, Richter A, Baier K, Meyer J, et al. Four-dimensional treatment planning for stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2007;69:276–85.
[19] Lacornerie T, Lisbona A, Mirabel X, Lartigau E, Reynaert N. GTV-based prescription in SBRT for lung lesions using advanced dose calculation algorithms. Radiat Oncol 2014;9:223.
[20] Swaminath A, Massey C, Brierley JD, Dinniwell R, Wong R, Kim JJ, et al. Accumulated delivered dose response of stereotactic body radiation therapy for liver metastases. Int J Radiat Oncol 2015;93:639–48.
[21] Andratschke N, Parys A, Stadtfeld S, Wurster S, Huttenlocher S, Imhoff D, et al. Clinical results of mean GTV dose optimized robotic guided SBRT for liver metastases. Radiat Oncol 2016;11:74.
[22] Klement RJ, Allgäuer M, Andratschke N, Blanck O, Boda-heggemann J, Dieckmann K, et al. Bayesian cure rate modeling of local tumor control: evaluation in stereotactic body radiotherapy for pulmonary metastases. Int J Radiat Oncol 2016;94:841–9.
[23] Landriscina M, Maddalena F, Laudiero G, Esposito F. Adaptation to oxidative stress, chemoresistance, and cell survival. Antioxid Redox Signal 2009;11:2701–16.
[24] Fink MK, Kleeberg UR, Bartels S. Adjuvant therapy-related shortening of survival (ATRESS): an underrated phenomenon. Oncologist 2015;20:88.
[25] Ahmed KA, Caudell JJ, El-Haddad G, Berglund AE, Welsh EA, Yue B, et al. Radiosensitivity differences between metastases based on primary histology suggest implications for clinical outcomes follwoing SBRT. Int J Radiat Oncol Biol Phys 2016.
[26] Takeda A, Kunieda E, Ohashi T, Aoki Y, Koike N, Takeda T. Stereotactic body radiotherapy (SBRT) for oligometastatic lung tumors from colorectal cancer and other primary cancers in comparison with primary lung cancer. Radiother Oncol 2011;101:255–9.
[27] Thibault I, Poon I, Yeung L, Erler D, Kim A, Keller B, et al. Predictive factors for local control in primary and metastatic lung tumours after four to five fraction stereotactic ablative body radiotherapy: a single institution's comprehensive experience. Clin Oncol (R Coll Radiol) 2014;26:713–9.
[28] Binkley MS, Trakul N, Jacobs LR, Von Eyben R, Le Q-TT, Maxim PG, et al. Colorectal histology is associated with an increased risk of local failure in lung metastases treated with stereotactic ablative radiation therapy. Int J Radiat Oncol Biol Phys 2015;92:1044–52.
[29] Guckenberger M, Wulf J, Mueller G, Krieger T, Baier K, Gabor M, et al. Dose–response relationship for image-guided stereotactic body radiotherapy of pulmonary tumors: relevance of 4D dose calculation. Int J Radiat Oncol Biol Phys 2009;74:47–54.
[30] Filippi AR, Badellino S, Ceccarelli M, Guarneri A, Franco P, Monagheddu C, et al. Stereotactic ablative radiation therapy as first local therapy for lung oligometastases from colorectal cancer: a single-institution cohort study. Int J Radiat Oncol 2015;91:524–9.
[31] Fode MM, Høyer M. Survival and prognostic factors in 321 patients treated with stereotactic body radiotherapy for oligo-metastases. Radiother Oncol 2015;114:155–60.
[32] Guckenberger M, Klement RJ, Allgäuer M, Andratschke N, Blanck O, Boda-heggemann J, et al. Local tumor control probability modeling of primary and secondary lung tumors in stereotactic body radiotherapy. Radiother Oncol 2016;118:485–91.
[33] Milano MT, Katz AW, Zhang H, Okunieff P. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. Int J Radiat Oncol Biol Phys 2012;83:878–86.
[34] Qi XS, White J, Li XA. Is α/β for breast cancer really low? Radiother Oncol 2011;100:282–8.